

**WHAT IS CLAIMED IS:**

1. A method of treating or preventing pain comprising administering to a mammal in need thereof a therapeutically effective amount of (a) an opiate analgesic and (b) a therapeutically effective amount of a calcium calmodulin dependent protein kinase (CaMKII) inhibitor.
2. The method of claim 1 wherein the opiate analgesic and CaMKII inhibitor are administered simultaneously.
3. The method of claim 2 wherein the opiate analgesic and CaMKII inhibitor are administered from a single composition.
4. The method of claim 2 wherein the opiate analgesic and CaMKII inhibitor are administered from separate compositions.
5. The method of claim 1 wherein the opiate analgesic and CaMKII inhibitor are administered sequentially.
6. The method of claim 5 wherein the opiate analgesic is administered prior to the CaMKII inhibitor.

7. The method of claim 5 wherein the CaMKII inhibitor is administered prior to the opiate analgesic.

8. The method of claim 1 wherein the opiate analgesic is selected from the group consisting of an opium alkaloid, a semisynthetic opiate analgesic, and a mixture thereof.

9. The method of claim 1 wherein the opiate analgesic is selected from the group consisting of opium, morphine, morphine sulfate, codeine, codeine phosphate, codeine sulfate, diacetylmorphine, morphine hydrochloride, morphine tartrate, diacetylmorphine hydrochloride, dextromethorphan hydrobromide, hydrocodone bitartrate, hydromorphone, hydromorphone hydrochloride, levorphanol tartrate, oxymorphone hydrochloride, oxycodone hydrochloride, fentanyl, meperidine, methadone, propoxyphene, and mixtures thereof.

10. The method of claim 1 wherein the opiate analgesic comprises morphine or a salt thereof.

11. The method of claim 1 wherein the CaMKII inhibitor comprises a CaMKII $\alpha$  inhibitor.

12. The method of claim 1 wherein the CaMKII inhibitor comprises a calcium chelator, a calmodulin antagonist, a small peptide based on CaMKII protein sequence, a nucleic acid-based inhibitor, and mixtures thereof.

13. The method of claim 1 wherein the CaMKII inhibitor is selected from the group consisting of KN62, KN93, H89, HA1004, HA1077, autocamtide-2 related inhibitory peptide or a myristoylated form thereof, K-252a, staurosporine, lavendustin C, BAPTA tetrasodium salt, 5,5'-dibromo-BAPTA, tetrasodium salt, BAPTA/AM, 5,5'-difluoro-BAPTA/AM, EDTA tetrasodium salt, EGTA, EGTA/AM, MAPTAM, TPEN, calmidazolium chloride, calmodulin binding domain, chlorpromazine, Compound 48/80, fluphenazine-N-2-chloroethane dihydrochloride, melittin, ophiobolin A, pentamidine isethionate, phenoxybenzamine, trifluoperazine, W-5, W-7, W-12, W-13, CaM kinase II 290-309, [Ala286]CaMKII Inhibitor 281-301, CaMKII Inhibitor 281-309, and mixtures thereof.

14. The method of claim 1 wherein the CaMKII inhibitor comprises a nucleic acid-based inhibitor capable of modulating expression of CaMKII and selected from the group consisting of an anti-sense polynucleotide, a ribozyme, RNAi, a triple helix polynucleotide, and mixtures thereof.

15. The method of claim 1 wherein the opiate analgesic is administered at a dose lower than a dose of the same opiate analgesic administered alone to achieve a predetermined reduction of pain.

16. The method of claim 1 wherein the treatment or prevention of pain has a longer duration than a treatment that administers the opiate analgesic alone.

17. The method of claim 1 wherein the mammal is a human.

18. The method of claim 1 wherein the pain is chronic pain.

19. The method of claim 18 wherein the chronic pain is selected from the group consisting of cancer pain, post-traumatic pain, post-operative pain, neuropathic pain, and pain associated with a myocardial infarction.

20. A method of reducing, reversing, or preventing tolerance to an opiate analgesic in an individual undergoing opiate analgesic therapy comprising administering a therapeutically effective amount of a calcium calmodulin dependent protein kinase inhibitor to the individual.

21. The method of claim 20 wherein the tolerance is established.

22. A method of reversing or preventing dependence on an opiate analgesic in an individual undergoing opiate analgesic therapy comprising administering a therapeutically effective amount of a calcium calmodulin dependent protein kinase inhibitor to the individual.

23. A method of treating opiate analgesic withdrawal comprising administering to an individual in need thereof a therapeutically effective amount of a calcium calmodulin dependent protein kinase inhibitor.

24. A composition comprising (a) a calcium calmodulin dependent protein kinase inhibitor, (b) an opiate analgesic, and (c) an excipient.

25. The composition of claim 24 wherein the CaMKII inhibitor comprises KN93, KN62, CaMKII Inhibitor 281-309, and mixtures thereof.

26. The composition of claim 24 wherein the opiate analgesic comprises morphine.

27. A method of identifying an inhibitor of calcium calmodulin kinase comprising administering a candidate compound to a morphine-tolerant mammal and monitoring calcium calmodulin kinase expression in the mammal, wherein calcium calmodulin kinase expression is less in presence of the candidate compound than in the absence of the candidate compound.